LOW DOSE IONIZING RADIATION EXPOSURE AND CARDIOVASCULAR DISEASE MORTALITY: COHORT STUDY BASED ON CANADIAN NATIONAL DOSE REGISTRY OF RADIATION WORKERS

JAN M. ZIELINSKI1,2, PATRICK J. ASHMORE3, PIERRE R. BAND1, HUIXIA JIANG3, NATALIA S. SHILNIKOVA3, VALERIE K. TAIT3, and DANIEL KREWSKI3

1 Health Canada, Ottawa, Ontario, Canada
2 University of Ottawa, Ontario, Canada
3 University of Ottawa, Ontario, Canada

Abstract

Objectives: The purpose of our study was to assess the risk of cardiovascular disease (CVD) mortality in a Canadian cohort of 337,397 individuals (169,256 men and 168,141 women) occupationally exposed to ionizing radiation and included in the National Dose Registry (NDR) of Canada.

Material and Methods: Exposure to high doses of ionizing radiation, such as those received during radiotherapy, leads to increased risk of cardiovascular diseases. The emerging evidence of excess risk of CVDs after exposure to doses well below those previously considered as safe warrants epidemiological studies of populations exposed to low levels of ionizing radiation. In the present study, the cohort consisted of employees at nuclear power stations (nuclear workers) as well as medical, dental and industrial workers. The mean whole body radiation dose was 8.6 mSv for men and 1.2 mSv for women.

Results: During the study period (1951–1995), as many as 3,533 deaths from cardiovascular diseases have been identified (3,018 among men and 515 among women). In the cohort, CVD mortality was significantly lower than in the general population of Canada. The cohort showed a significant dose response both among men and women. Risk estimates of CVD mortality in the NDR cohort, when expressed as excess relative risk per unit dose, were higher than those in most other occupational cohorts and higher than in the studies of Japanese atomic bomb survivors.

Conclusions: The study has demonstrated a strong positive association between radiation dose and the risk of CVD mortality. Caution needs to be exercised when interpreting these results, due to the potential bias introduced by dosimetry uncertainties, the possible record linkage errors, and especially by the lack of adjustment for non-radiation risk factors.

Key words: Ionizing radiation, Low doses, Cardiovascular disease mortality

INTRODUCTION

Extensive research into diseases of the cardiovascular system, a major cause of mortality and morbidity in both industrialized and developing countries, has identified multiple risk factors for these diseases [1–2]. It has long been known from experimental animal studies and epidemiological studies of radiotherapy patients that ionizing radiation exposure at doses in the order of tens of Gy increases the risk of cardiovascular diseases [3–6]. More recently, the study of Japanese atomic bomb survivors provided evidence that the excess risk of cardiovascular diseases (CVDs) can be associated with doses below 4 Gy...
In A-bomb survivors, the association between radiation and the risk of CVDs is likely to be causal as it cannot be explained by confounding, selection bias, or disease misclassification on death certificates [4]. Epidemiologic studies of CVDs in populations exposed to lower levels of ionizing radiation, such as those in occupational settings, do not provide conclusive evidence of a radiation-related risk of these diseases, and further research is needed to characterize the possible risk at low radiation doses [10–11]. An earlier analysis within a cohort study of the National Dose Registry (NDR) of Canada [12] showed a statistically significant positive excess relative risk (ERR) of 2.3 and 90% confidence interval (90% CI: 0.9–3.7) for CVD mortality among 105,456 male cohort members exposed to ionizing radiation between 1951 and 1983. This paper presents the results of analysis of CVD mortality in an updated cohort (169,256 males, 168,141 females) with exposures between 1951 and 1995.

METHODS

Data Sources
The NDR of Canada is described in detail elsewhere [12–13]. Briefly, the database is maintained by the Radiation Protection Bureau of the Government of Canada and contains basic identifying information and records of radiation exposures for all workers monitored in Canada since 1951. Reports of radiation exposure are routinely received from the Canadian National Dosimetry Services, commercial dosimetry services, Atomic Energy of Canada Limited (AECL), nuclear power generating facilities as well as mining operations. During the study period between January 1, 1951, and December 31, 1995, there were 438,373 subjects registered in the NDR. Vital status and causes of death were determined via probabilistic linkage to the Canadian Mortality Database (CMDB). This database records all deaths in Canada since 1950. Causes of death were re-coded according to the International Classification of Diseases, ninth revision (ICD-9) [14]. The analysis included all cardiovascular diseases: ICD-9 codes 390-459. Vital status was confirmed by linkage to tax records.

Record Linkage
A probabilistic generalized record linkage system developed by the Statistics Canada was used to link records in the NDR with the CMDB [15–17]. The linkage methodology has been described comprehensively elsewhere [12].

Dosimetry
A description of the external dosimetry used among the contributors to the NDR has been provided by Ashmore et al. [12]. The dosimeters used, monitoring frequencies, and reporting thresholds have varied throughout the study period as previously described [12,18]. External whole body doses could include exposures to X rays, γ rays, β particles, and neutrons. The quality factors applied to these exposures for dose assessment in the NDR cohort were 1, 1, 1 and 10, respectively. Internal exposures to tritium, found mainly among nuclear workers, were determined from measurement of urinary levels. In this study, the whole body dose estimates included the contribution from tritium, but excluded that from neutrons or from other radionuclides as they were considered negligible [12].

Statistical Analysis
Occupational categories were defined based on the job class codes in the NDR. Employees at nuclear power stations constituted the nuclear workers category. The dental workers category included dental assistants, hygienists and dentists. Physicians, radiologists, radiology and nuclear medicine technicians, radiotherapists, nurses and orderlies were assigned to the medical workers category. The industrial workers category contained a range of occupations: industrial radiographers, engineers, university and government employees, AECL employees, and veterinarians and veterinary assistants. In the first mortality analysis of the NDR cohort, six categories of the socio-economic status (SES) based on job type were defined: professional, intermediate, skilled non-manual, skilled manual, partly skilled and unskilled. Standardized mortality ratios were calculated to compare CVD mortality in the NDR cohort and in the general population of Canada. Age, gender, calendar year and cause-specific ratios were determined, and confidence intervals were calculated assuming the
observed number of deaths exhibited a Poisson distribution [19]. Poisson regression techniques were used to estimate hazard rates and the effect of radiation exposure on these rates. Excess relative risk (ERR) was modeled assuming a linear dose response function:

$$\lambda(s,a,b,j,e,d) = \lambda_o(s,a,b,j) \times [1.0 + \text{ERR} \times d \times \exp(\Sigma z_i z_j)] \quad (1)$$

where $\lambda_o$ was the baseline hazard rate that was assumed to depend on sex ($s$) and attained age ($a$), year of birth ($b$), and occupational category ($j$); $\lambda(s, a, b, j, e, d)$ was the rate at the cumulative lagged dose ($d$), and ERR was the excess relative risk with potential multiplicative modifying effects ($z_i$) of age at exposure ($e$), sex ($s$) and attained age ($a$). The model for excess absolute risk (EAR) was a follows:

$$\lambda(s,a,b,j,e,d) = \lambda_o(s,a,b,j) + \text{EAR}(s,a,e,d) \quad (2)$$

where $\lambda_o$ was the baseline hazard rate adjusted for sex ($s$), attained age ($a$), year of birth ($b$) and occupational category ($j$). EAR ($d,e,s,a$) was the absolute change between the rate associated with cumulative lagged dose ($d$) and the rate associated with zero dose. Age at exposure ($e$), sex ($s$) and attained age ($a$) were included as potential effect modifiers. The EPICURE software [20] was used to estimate the study parameters and carry out significance testing. Significance tests were based on $\chi^2$ approximations to the distribution of likelihood ratio tests. In the cases where a likelihood required an ERR below the minimum value of $1/D_{\text{max}}$ ($D_{\text{max}} =$ maximum dose for individual cell), no convergence was obtained [18]. Doses were lagged 10 years.

The relationships between the measured external dose of ionizing radiation and the relative risk for different causes of death were also investigated by trend analysis, with the doses subdivided into nine dose categories (0, 0–4.9, 5–9.9, 10–19.9, 20–49.9, 50–99.9, 100–199.9, 200–399.9, > 400 mSv). The significance of the trend was tested using ERR fit [19].

RESULTS

Of the 438 373 subjects registered in the NDR as of December 31, 1995, as much as 23% were excluded from the analysis. The reasons for exclusion were insufficient identifying information for record linkage and missing information on gender or year of birth. Also, miners were excluded because the radiation exposure records based on personal dosimeters were only available since 1980. Of the 337 397 subjects retained in the analysis, 10 888 were linked with the CMDB. The number of deaths from CVDs was 3 533 (3 018 among males and 515 among females). Table 1 shows the characteristics of the cohort ($n = 337,397$). Almost 50% of the cohort were females and the mean duration of follow-up was 15 years. The mean duration for males was 16.5 years. The mean age at death was 58.5 for males and 52.5 for females.

A distribution of cumulative whole body doses received by the cohort members is provided in Table 2. Twelve percent and three percent of males and females, respectively, received more than 10 mSv during the follow-up period. The mean age at first exposure was 30 years for males and 26 years for females and the mean age at which monitoring ended was 46.6 and 41 years for males and females, respectively (Table 1). The CVD mortality

| Table 1. Characteristics of the National Dose Registry cohort (1951–1995) |
|-----------------------------|-----------------------------|-----------------------------|
| Characteristics             | Males                       | Females                     | Total                       |
|                             | n                           | %                          | n                           | %                          |
| Sex                         | 169 256.00                  | 50.2                       | 168 141.00                  | 49.8                       | 337 397.00                  | 100.0                       |
| Mean duration of follow-up (years) | 16.50                       | –                          | 15.00                       | –                          | 15.80                       | –                          |
| Mean age at death (years)    | 58.50                       | –                          | 52.50                       | –                          | 55.50                       | –                          |
| Mean age at onset of monitored exposure (years) | 30.10                       | –                          | 26.00                       | –                          | 28.00                       | –                          |
| Mean age at end of monitored exposure (years) | 46.60                       | –                          | 41.00                       | –                          | 43.80                       | –                          |
| Mean cumulative dose (mSv)   | 8.55                        | –                          | 1.22                        | –                          | 4.90                        | –                          |
The study confirms our previous finding of a significant association between radiation exposure and CVD mortality in men [12]. For women, the previously observed association [12] has become statistically significant. Owing to the smaller number of deaths among women in the higher dose categories, compared to men (Table 2), the ERR/Sv for women has a wider confidence interval.

The considerations of the strengths and limitations of this study are important for the interpretation of results. The strength of the study is that it provides direct estimates of health risks from long-term low-level radiation exposure which are based on the largest national cohort of radiation workers (nearly 340,000 individuals) with a long follow-up of mortality (up to 45 years) and dose estimates based on individual monitoring.

The major limitation of this study, as in most other occupational studies, is the absence of information on non-radiation lifestyle-related CVD risk factors, such as smoking, excessive alcohol consumption, diet, and other factors. The lack of adjustment for these factors in the dose-response analysis may lead to confounding if they positively correlate with radiation dose. This may be the case, at least in part, for smoking in the NDR cohort [18]. To adjust for the potential confounding effect of non-radiation risk factors, SES variable could be used as surrogate.

Research studies have shown that mortality from various in the cohort was significantly lower than in the Canadian population at large, with the standardized mortality ratio (SMR) of 0.59 (90% CI: 0.57, 0.61) for males and of 0.50 (90% CI: 0.46, 0.54) for females. In comparison with the general population, the cohort exhibited a healthy worker effect with respect to CVDs.

Relative Risks (RRs) of cardiovascular diseases by dose category are presented in Fig. 1 and Table 3, and the ERR, EAR and attributable risk (AR) are shown in Table 4. A significant dose response is evident in the ERR for men and women (1.22, 90% CI: 0.47, 2.10 and 7.4; 90% CI: 0.95, 18.1, respectively). The excess absolute risk for the whole cohort was 37.5 per Sievert per 10,000 person-years (90% CI: 17.0, 60.1).

**DISCUSSION**

The present analysis of CVD mortality in the NDR cohort has been conducted based on extended cohort (by about 130,000 individuals) and follow-up (by 8 years) compared to our previous mortality study [12]. The extensions have almost doubled the number of deaths from CVDs available for the analysis. As in our previous study and many other studies of occupational cohorts, a strong healthy worker effect has been detected, with the mortality in the NDR cohort being about 40% and 50% lower than that in the general Canadian population, respectively for the male and female cohort members. The study confirms our previous finding of a significant association between radiation exposure and CVD mortality in men [12]. For women, the previously observed association [12] has become statistically significant. Owing to the smaller number of deaths among women in the higher dose categories, compared to men (Table 2), the ERR/Sv for women has a wider confidence interval.

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bomb survivors. Preston et al. [9] reported an ERR/Sv of 0.17 for heart disease (90% CI: 0.08, 0.26) and 0.12 for stroke (90% CI: 0.02, 0.22) in the atomic bomb survivors. These estimates are substantially lower and statistically in-
compatible with the ERR/Sv of 1.35 (90% CI: 0.59, 2.24) calculated in our study.

In the international 15-country study of radiation workers, there is little evidence for an association between diseases is a function of SES [21]. However, SES information was available only for a half of the cohort members; consequently, it was not used in the present analysis. In view of this, the strong association between radiation exposure and CVD risk demonstrated in the NDR cohort should be interpreted with caution. Indeed, the risk estimates in our study are higher than those in most other occupational cohorts [10–11] and in the Japanese atomic

Table 3. Relative Risk (RR) of CVD mortality by dose category in the NDR cohort (1951–1995)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Dose category (mSv)</th>
<th>0</th>
<th>&gt; 0</th>
<th>5–</th>
<th>10–</th>
<th>20–</th>
<th>50–</th>
<th>100–</th>
<th>200–</th>
<th>400–</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean dose (mSv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>Observed deaths</td>
<td>1437.00</td>
<td>883.00</td>
<td>156.00</td>
<td>148.00</td>
<td>166.00</td>
<td>102.00</td>
<td>58.00</td>
<td>46.00</td>
<td>22.00</td>
</tr>
<tr>
<td></td>
<td>Expected deaths</td>
<td>1481.60</td>
<td>877.90</td>
<td>139.10</td>
<td>130.20</td>
<td>157.00</td>
<td>83.50</td>
<td>52.90</td>
<td>33.40</td>
<td>14.20</td>
</tr>
<tr>
<td></td>
<td>Fitted</td>
<td>1481.60</td>
<td>879.20</td>
<td>140.30</td>
<td>132.50</td>
<td>163.10</td>
<td>90.60</td>
<td>61.90</td>
<td>45.10</td>
<td>23.70</td>
</tr>
<tr>
<td></td>
<td>Observed RR</td>
<td>1.00</td>
<td>1.04</td>
<td>1.16</td>
<td>1.17</td>
<td>1.09</td>
<td>1.26</td>
<td>1.13</td>
<td>1.42</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>Fitted RR</td>
<td>1.00</td>
<td>1.00</td>
<td>1.01</td>
<td>1.02</td>
<td>1.04</td>
<td>1.08</td>
<td>1.17</td>
<td>1.35</td>
<td>1.67</td>
</tr>
<tr>
<td>Females</td>
<td>Observed</td>
<td>288.00</td>
<td>156.00</td>
<td>30.00</td>
<td>17.00</td>
<td>14.00</td>
<td>5.00</td>
<td>5.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Expected</td>
<td>288.40</td>
<td>165.70</td>
<td>21.30</td>
<td>12.00</td>
<td>10.50</td>
<td>3.40</td>
<td>2.20</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fitted</td>
<td>288.40</td>
<td>167.00</td>
<td>22.40</td>
<td>13.20</td>
<td>12.90</td>
<td>5.10</td>
<td>5.90</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Observed RR</td>
<td>1.00</td>
<td>0.90</td>
<td>1.40</td>
<td>1.40</td>
<td>1.30</td>
<td>1.50</td>
<td>2.30</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fitted RR</td>
<td>1.00</td>
<td>1.01</td>
<td>1.05</td>
<td>1.10</td>
<td>1.23</td>
<td>1.51</td>
<td>2.68</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Both</td>
<td>Mean dose (mSv)</td>
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<td>1.10</td>
<td>7.10</td>
<td>14.10</td>
<td>31.40</td>
<td>70.20</td>
<td>139.90</td>
<td>271.80</td>
<td>553.80</td>
</tr>
<tr>
<td></td>
<td>Observed deaths</td>
<td>1725.00</td>
<td>1039.00</td>
<td>186.00</td>
<td>165.00</td>
<td>180.00</td>
<td>107.00</td>
<td>63.00</td>
<td>46.00</td>
<td>22.00</td>
</tr>
<tr>
<td></td>
<td>Expected</td>
<td>1770.40</td>
<td>1046.80</td>
<td>161.00</td>
<td>142.40</td>
<td>167.80</td>
<td>86.90</td>
<td>54.50</td>
<td>33.50</td>
<td>14.40</td>
</tr>
<tr>
<td></td>
<td>Fitted</td>
<td>1770.40</td>
<td>1047.60</td>
<td>162.50</td>
<td>154.00</td>
<td>175.00</td>
<td>95.10</td>
<td>64.80</td>
<td>46.40</td>
<td>25.10</td>
</tr>
<tr>
<td></td>
<td>Observed RR</td>
<td>1.00</td>
<td>1.02</td>
<td>1.19</td>
<td>1.19</td>
<td>1.10</td>
<td>1.26</td>
<td>1.15</td>
<td>1.44</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>Fitted RR</td>
<td>1.00</td>
<td>1.00</td>
<td>1.01</td>
<td>1.02</td>
<td>1.04</td>
<td>1.09</td>
<td>1.19</td>
<td>1.39</td>
<td>1.75</td>
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</tbody>
</table>

![Fig. 1. Odds ratios for CVD mortality and 90% confidence intervals by dose category (as in Table 2) in the NDR cohort (1951–1995).](image-url)

![Table 4. Excess Relative Risk (ERR), Excess Absolute Risk (EAR), and Attributable Risk (AR) in the NDR cohort (1951–1995).](table-url)
CVD mortality and radiation dose (ERR/Sv = 0.09, 95% CI: –0.43, 0.70) [22]. A statistically significant association, with ERR/Sv of 0.65 (90% CI: 0.36, 0.98), has recently been reported in a large cohort of workers at the British Nuclear Fuels [23]. However, the authors concluded that their results were not consistent with a simple causal interpretation and that further studies were required, including investigation of the possible role of the factors associated with the socio-economic status.

The other potential sources of bias in our study are dosimetry uncertainties and the possible record linkage errors. The dosimetry system used in the NDR met the quality criteria when assessed by the dosimetry committee of the international collaborative IARC study [24–25]. Of concern in the NDR study are the uncertainties related to recording doses below the dosimeter detection limit as zero. This may lead to an underestimation of radiation exposure and, consequently, to an overestimation of the related health risks. To address this concern, a study was conducted by Shin et al. [26], which indicated that this type of dose error is unlikely to result in an overestimation of risk by more than 15–20%. The findings of the theoretical study by Krewski et al. [27] suggest that record linkage errors can introduce bias into the estimates of SMR and relative risk regression coefficient, as well as an additional uncertainty into these estimates. Methods are to be developed to determine the direction and magnitude of this bias and to account for linkage errors in the statistical analyses of actual data.

A considerable proportion (23%) of subjects registered in the NDR over the study period (1951–1995) was excluded from the analysis. We do not believe, however, that this exclusion could bias the results because the reasons for exclusion were unrelated to the study outcome.

In the future, we are planning to conduct a study of CVD mortality in a cohort of more than 550 000 individuals registered in the NDR between 1951 and 2005, with a mortality follow-up extended through 2005. These extensions will result in a much larger number of cases available for the analysis and will allow us to conduct separate analyses of mortality from different groups of diseases within the broad category of cardiovascular diseases.

**CONCLUSION**

The present study provides direct estimates of the risk of cardiovascular diseases from long-term low-level radiation exposure which are based on the largest national cohort of radiation workers with a long-term mortality follow-up and individual dosimetry. The study has demonstrated a strong positive association between radiation dose and the risk of CVD mortality. Caution needs to be exercised in interpreting these results, due to the potential bias introduced by dosimetry uncertainties, potential record linkage errors, and, especially, by the lack of adjustment for non-radiation risk factors.

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**REFERENCES**


